Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 124, 125, 129-131 are pending in this application and are rejected on various grounds. Claim 124 has been amended to remove references to the functional recitation: "wherein, the nucleic acid encoding said polypeptide is amplified in squamous cell-type lung carcinomas or colon tumors." The rejections to the presently pending claims are respectfully traversed.

Claim Interpretation

Applicants agree with the Examiner's interpretation that the GenBank AB11112.1 sequence, or its variants, do not qualify as a polypeptide comprising the polypeptide of SEQ ID NO: 33 and therefore, the Examiner has rightly withdrawn the rejection drawn to Claim 124 and its dependents.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 124, 125 and 129-131 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility."

Claims 124, 125 and 129-131 remain further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

For the reasons outlined below, Applicants respectfully disagree.

Arguments

Applicants submit that the results of TaqMan™ PCR, reported in ΔCt units, are disclosed in the passage on page 539, lines 37-39 of the instant specification. As explained therein, one unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Applicants showed that the gene encoding for PRO290 was significantly amplified, that is, it showed approximately 1.22-2.07 ΔCt units which corresponds to $2^{1.22}$ -$2^{2.07}$- fold amplification or 2.297 fold to 4.2-fold amplification in five lung tumors and showed approximately 1.16-1.56

ΔCt units which corresponds to $2^{1.16}$ -$2^{1.56}$- fold amplification or 2.23 fold to 2.95-fold amplification in two colon tumors.

In support of their showing that these gene amplification values are significant, Applicants submit herewith, a Declaration by Dr. Audrey Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy (Emphasis added).

Accordingly, the 2.297 fold to 4.2-fold amplification in five lung tumors and the 2.23 fold to 2.95-fold amplification for colon cancer would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration. Thus, barring evidence to the contrary, Applicants maintain that the fold amplification disclosed for the PRO290 gene is significant and forms the basis for the utility claimed herein.

It is also well known that gene amplification occurs in most solid tumors, which includes lung and colon cancers, and is generally associated with poor prognosis. Therefore, the PRO290 gene becomes an important diagnostic marker to identify such malignant lung carcinomas, even if the lung or colon malignancy associated with PRO290 molecule is a rare occurrence.

The Utility Standard was discussed in detail in the previous response submitted August 20, 2004. Briefly, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant.

The Examiner had submitted references Pennica *et al.*, Haynes *et al.* and Konopka *et al.* to establish a prima facie case for lack of utility. Applicants respectfully submit that, the

combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added); thus a correlation was established for *WISP*-1. Similarly, in Konopka *et al.*, Applicants submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility. Therefore, a *prima facie* case for lack of utility has not been established based on Pennica *et al.* and Konopka *et al.*

Actually, the cited reference Haynes *et al.*, showed that "there was a general trend, although no strong correlation between protein [expression] and transcript levels." (see Figure 1 and page 1863, paragraph 2.1, last line). When the proper legal standard is used, this clearly supports Applicants' position. This is all that's needed to meet the "more likely than not" evidentiary standard. Again, *accurate prediction* is not the standard.

An additional point made by the Examiner in the Final Office action, at least on page 4, last four lines and page 5 is that:

> "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO290. There is no evidence regarding whether or not the PRO290 mRNA or polypeptide levels are also increased in these tumor samples.....it was imperative to find evidence in the relevant scientific literature...Given how small the DNA copy number of PRO290 increased, and the evidence provided by Haynes *et al.*, Pennica *et al.*, and Konopka *et al.*, it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels." (emphasis added).

Applicants strongly disagree. As discussed above, Applicants showed that the gene encoding for PRO290 was significantly amplified in certain lung and colon tumors. These values are considered significant based on the Declaration by Dr. Audrey Goddard discussed above. By referring to these significant values, namely 2.297 fold to 4.2-fold amplification in five lung tumors and the 2.23 fold to 2.95-fold amplification for colon cancer as "very small," the Examiner would be ignoring an expert's teachings within a declaration without any basis, or without presenting any evidence to the contrary. Applicants respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, barring evidence to the contrary, Applicants maintain that the fold amplification disclosed for the PRO290 gene is significant and forms the basis for the utility claimed herein.

Further, the Examiner seems concerned that data is provided "in a few tumor samples for PRO290."

Applicants submit that the fact that 5 lung tumors and 2 colon cancers tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO290 gene is amplified in five lung or two colon tumors or in most tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO290 is considered significant is what lends support to its usefulness as a tumor marker.

Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* (submitted with Applicants' Response filed August 20, 2004) collectively teach that in general, gene amplification increases mRNA expression. The results presented by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes.

Ornoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, this evidence supports the Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis (submitted with Applicants' Response filed August 20, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his

Declaration, shows that, in general, there is a correlation between increased mRNA and polypeptide levels.

Applicants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Applicants further submit that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Applicants' Response filed August 20, 2004) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Additional supporting evidence for such a utility is presented in a real-world example in an article by Hanna and Mornin (submitted with Applicants' Response filed August 20, 2004), which demonstrates a use for the breast cancer marker HER-2/neu. Hanna and Mornin teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH), as well as, the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Such testing is for the purpose of characterizing not the PRO290 polypeptide, but the tumors in which the gene encoding PRO290 is amplified. Therefore, the PRO290 polypeptide is also useful in tumor categorization, the results of which become an important tool in the hands of a physician

enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

The Examiner further cites the Hu *et al.* reference and concludes that:

> "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.....Hu *et al.* discovered that genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section)" (emphasis added).

Applicants respectfully submit that, contrary to the Examiner's assertion, the Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO290 molecule, for the reasons outlined below.

The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the

authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions do not represent genes in general.

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of one class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore summarizing the conclusions drawn so far, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these isolated instances do not satisfy the Utility standard where a showing that "it is more likely than not" must be made. Such a showing to establish a proper *prima facie* case for lack of utility has clearly not been done. On the contrary, in the majority of amplified genes in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration, etc. overwhelmingly show that gene amplification

influences gene expression at the mRNA and protein levels. Therefore, the references cited by the Examiner, namely, Pennica *et al.*, Konopka *et al.*, and Hu *et al.*, are not sufficient to establish a *prima facie* case of lack of utility since they do not teach anything whatsoever about the correlation of protein expression and gene amplification for genes in general. In fact, one of the Examiner's cited reference, Haynes *et al.* supports the Applicants position that gene amplification mostly correlates well with protein expression because **most** of the 80 diverse, yeast genes studied in Haynes showed some positive correlation (see Figure 1 of Haynes *et al.*). Therefore, one of skill in the art would reasonably expect, based on the amplification data for the PRO290 gene, that the PRO290 polypeptide is also concomitantly overexpressed. Even in the event that the PRO290 polypeptide were found not to be overexpressed in the lung or colon tumors where the PRO290 gene were amplified, (a position expressly not conceded to), the PRO290 polypeptide is still useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO290 polypeptides. Thus, Applicants request that the present 35 U.S.C. §101 rejection to the pending claims be withdrawn.

Further, Applicants respectfully submit that the skilled artisan would not have to perform undue experimentation in order to make or use PRO290 as a tumor marker based on the results of the gene amplification assay for the PRO290 gene and the state of the art in oncology at the time of filing of this application. Thus, Applicants request that the 35 U.S.C. §112, first paragraph enablement rejection also be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claim 124 is rejected under 35 U.S.C. §112, second paragraph for being indefinite.

In view of the cancellation of references to the rejected "wherein clause' in claim 124, Applicants submit that the claim is now definite and respectfully request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C3). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 2, 2005

On behalf of
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